SCHEME I

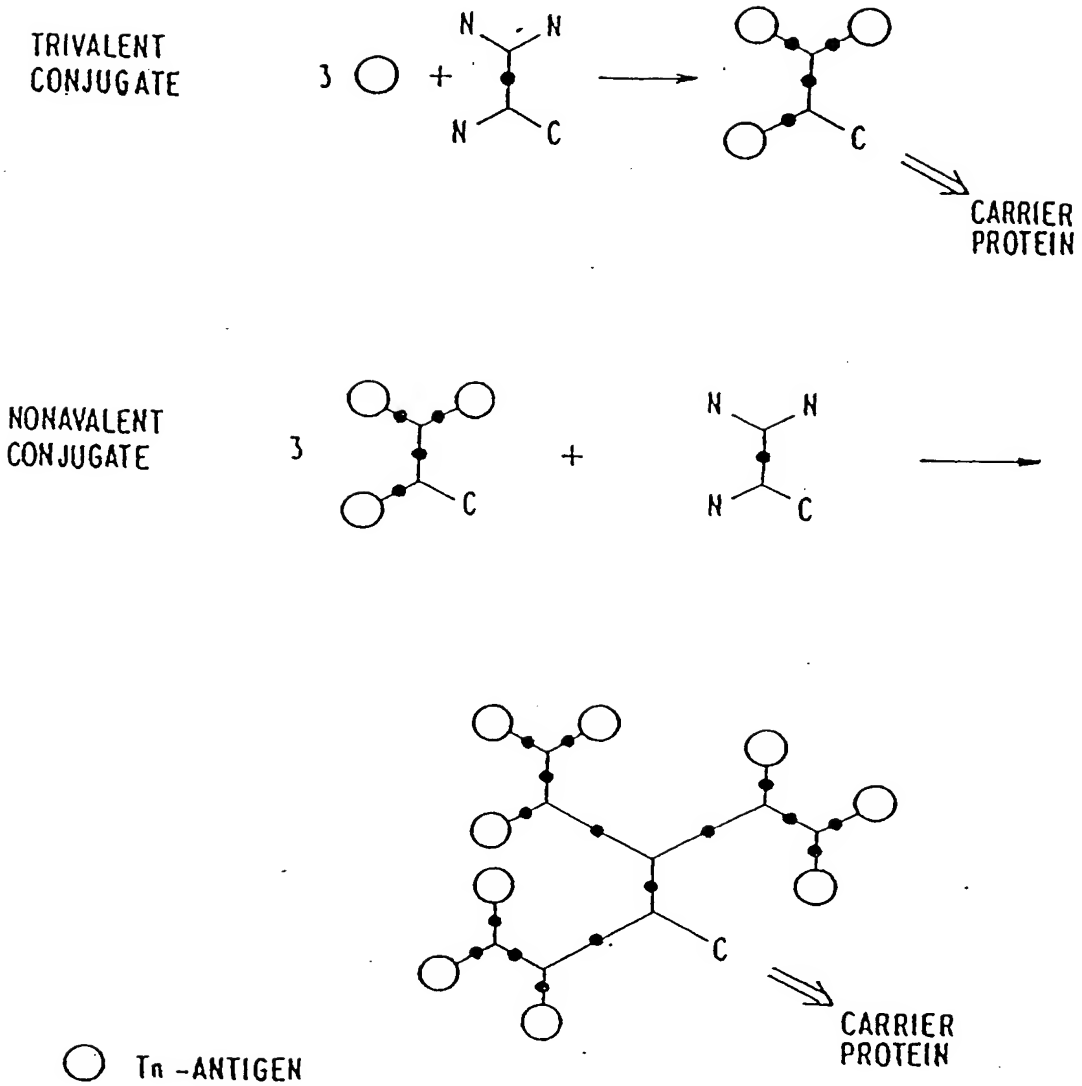
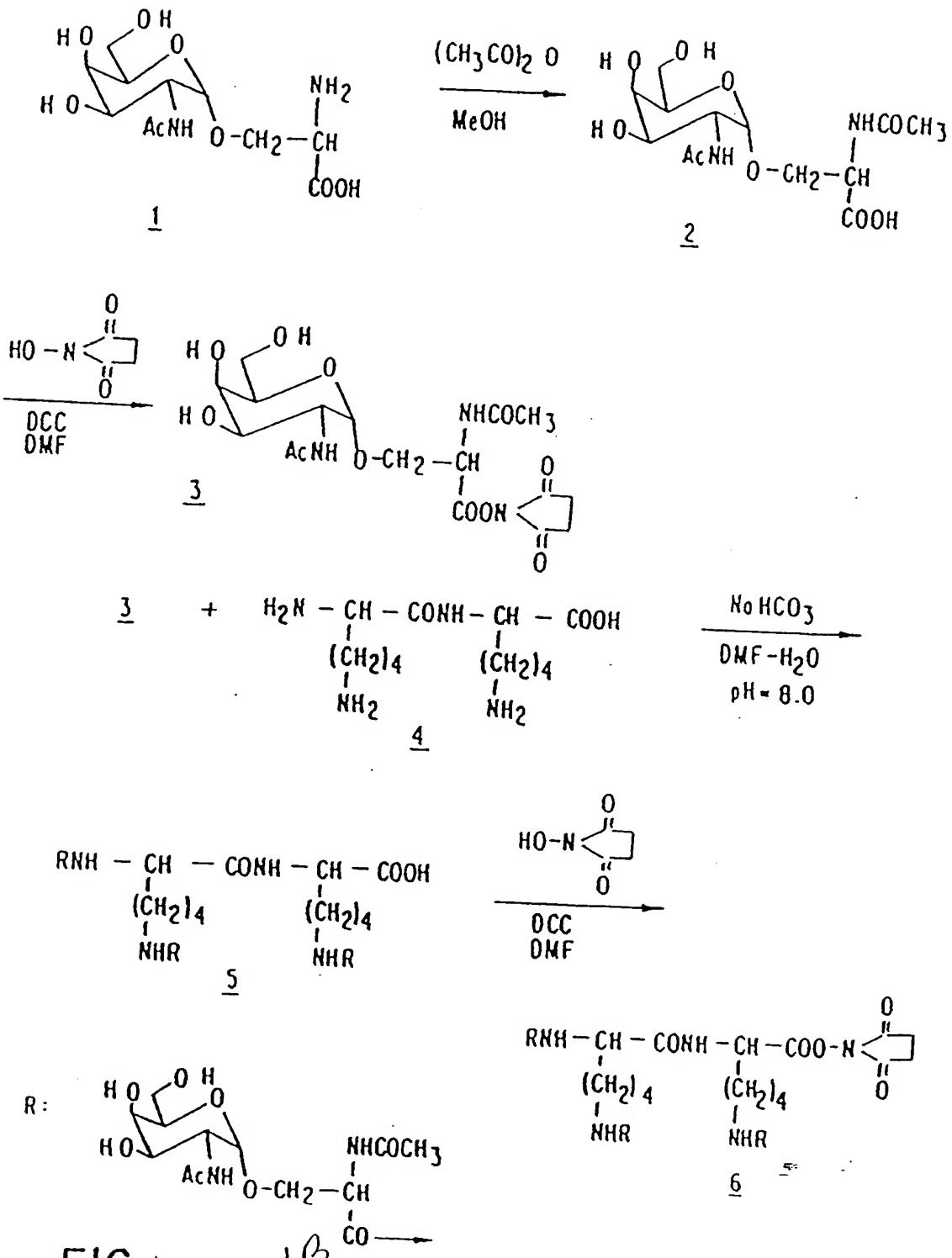


FIG. 1 A

SCHEME · II



1 2 3 4 5 6

FIG. 1B

SYNTHESIS OF ANTIGEN CLUSTERS.

General formula: $Ac-(Ser)_m-(Thr)_n-NH-(CH_2)_3-COOH$ $(m + n \leq 3)$

Examples:

$Ac-Ser-NH-(CH_2)_3-COOH$ 5
*

$Ac-Thr-NH-(CH_2)_3-COOH$
*

$Ac-Ser-Ser-NH-(CH_2)_3-COOH$
* *

$Ac-Ser-Ser-Ser-NH-(CH_2)_3-COOH$
* * *

$Ac-Ser-Thr-Thr-NH-(CH_2)_3-COOH$ 6
* * *

* : GalNAcα1 ⟶ /NeuAcα2 ⟶ 6GalNAcα1 ⟶

FIG. 2A

CONSTRUCTION OF MULTIVALENT SYSTEMS.

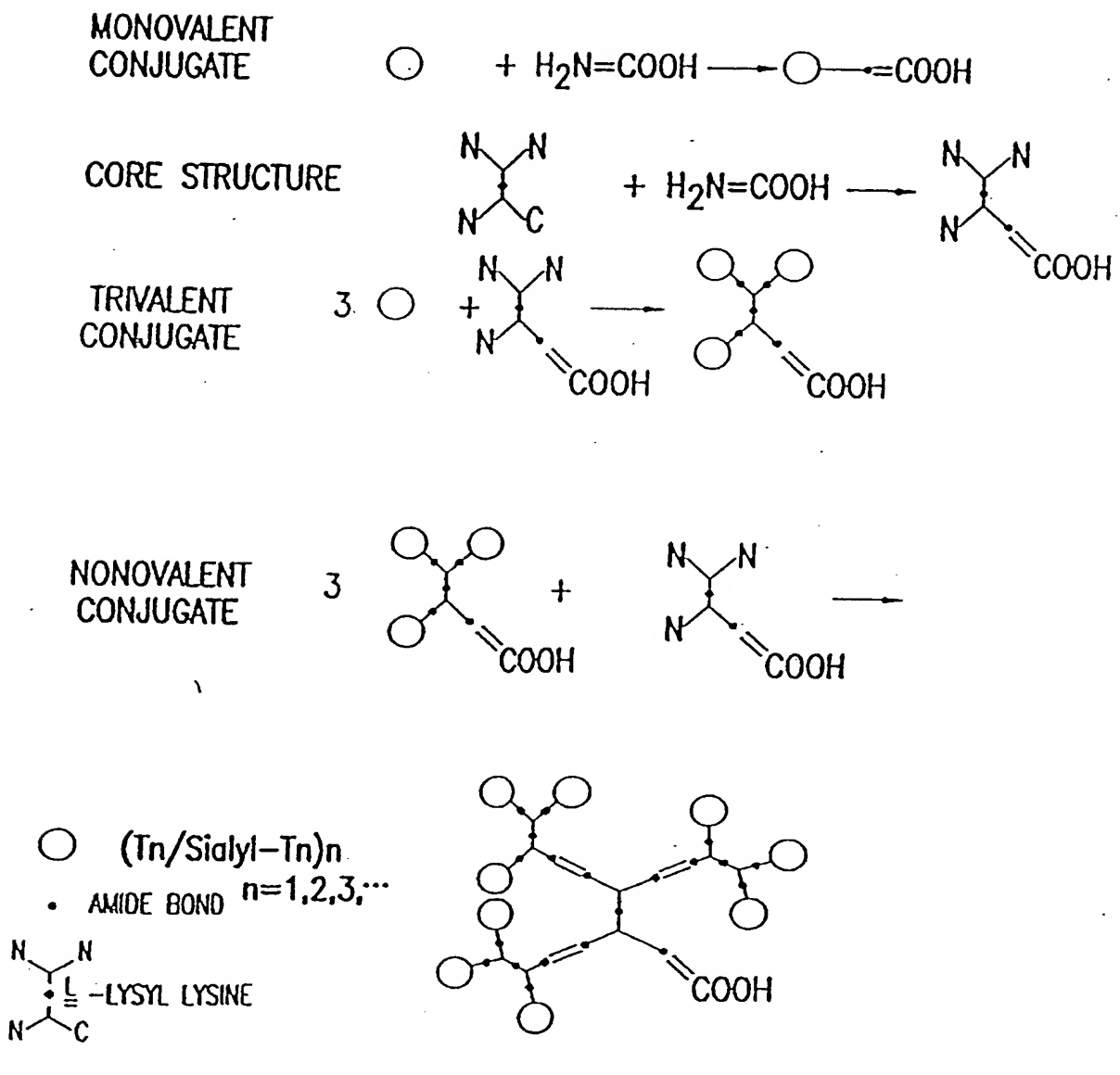


FIG. 2B

DESIGN FOR EFFECTIVE PRESENTATION OF SYNTHETIC ANTIGENS TO IMMUNE SYSTEM.

$(\square)_h$ —— carrier protein (e.g. BSA, KLH)

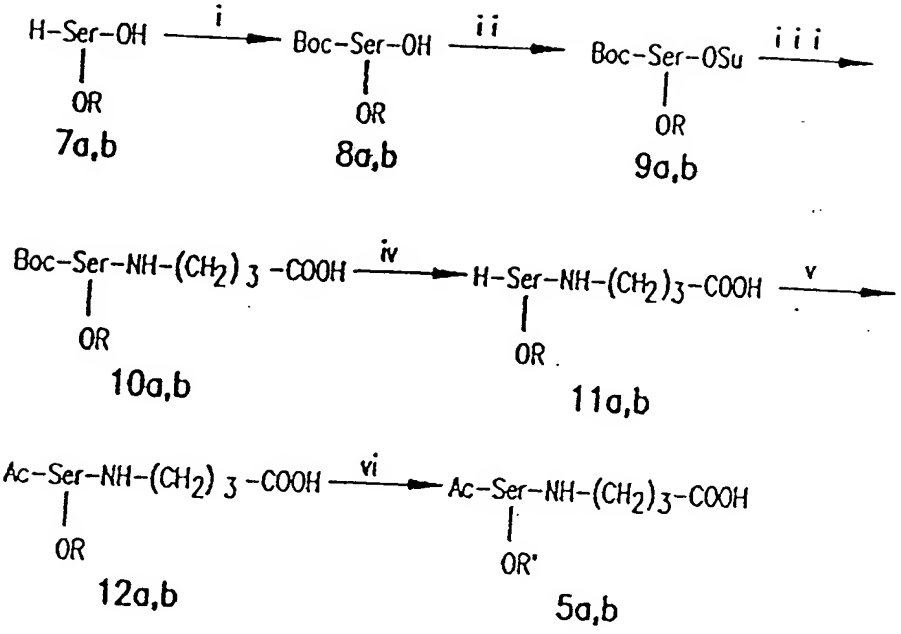
$\square$ —— tripalmitoyl–S–glycerylcysteinyl–seryl–serine

$\square$ —— monophosphoryl lipid A

$\square$: constructed antigen systems

FIG. 2c

SYNTHESIS OF 5



Reagents: i) Boc_2O, Et_3N, MeOH; i i) NHS, EDC, CH_2Cl_2;
i i i) $H_2N-(CH_2)_3-COOH$, Et_3N, DMF; iv) HCOOH; v) Ac_2O, MeOH;
vi) 10% 1N NaOH in MeOH, 5 min.

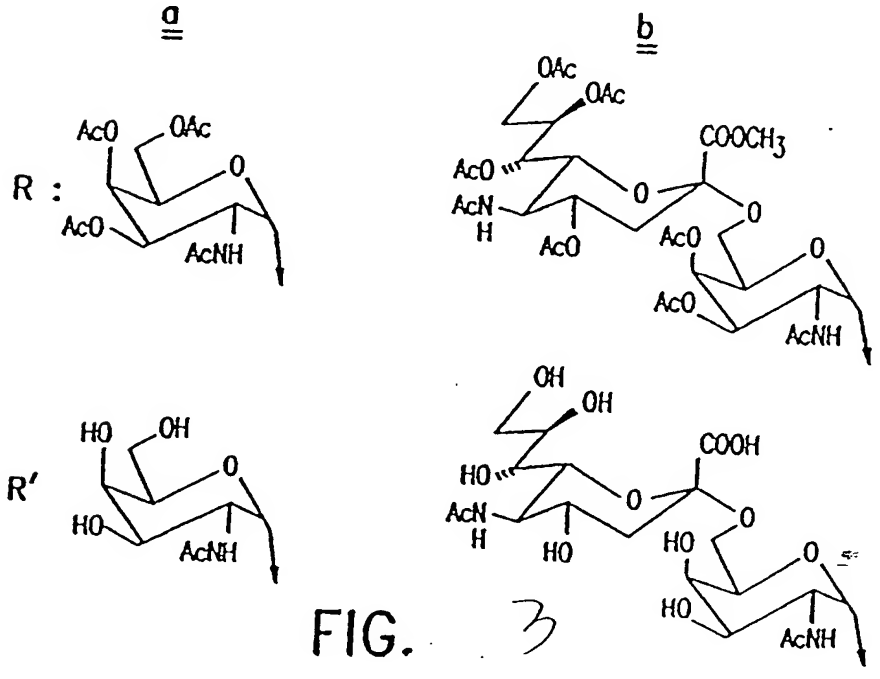
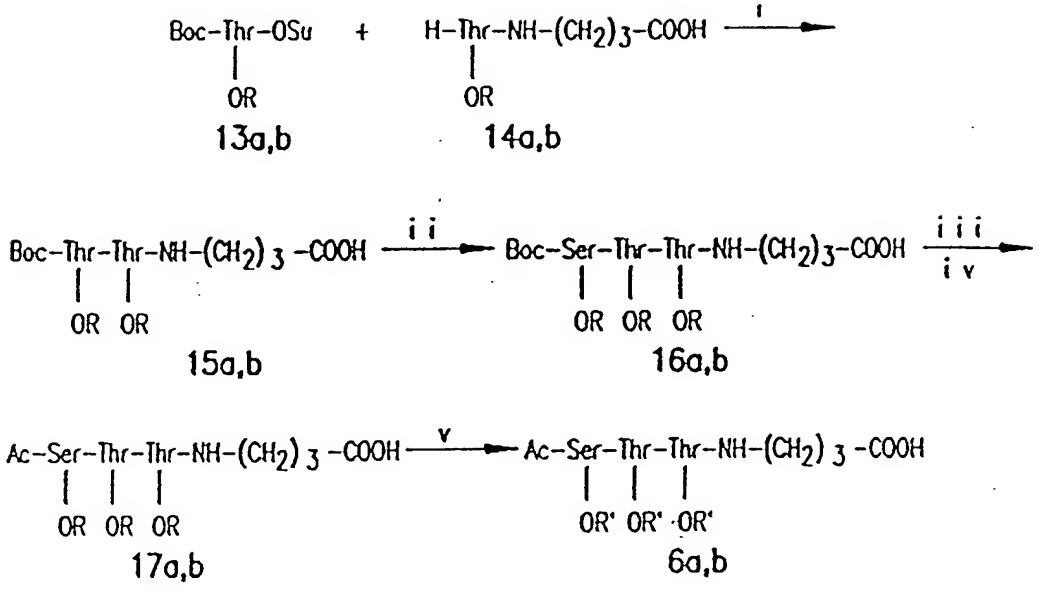


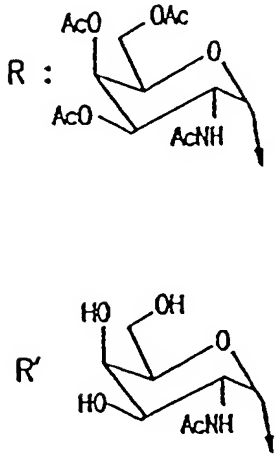
FIG. 3

SYNTHESIS OF 6



Reagents: i) Et_3N, DMF; i i) 9a,b ,Et_3N, DMF; i i i) HCOOH;
iv) Ac_2O, MeOH; v) 10% 1N NaOH in MeOH, 1 h.

a



b

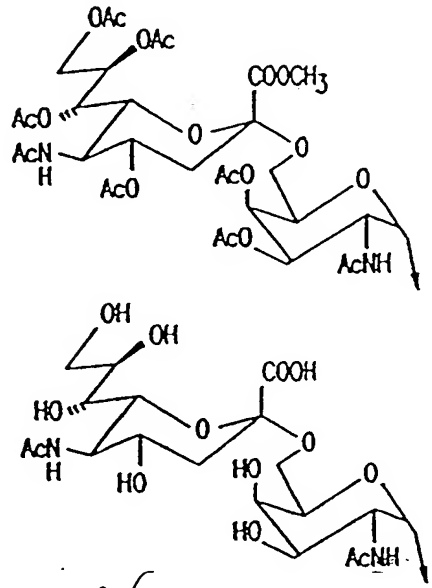
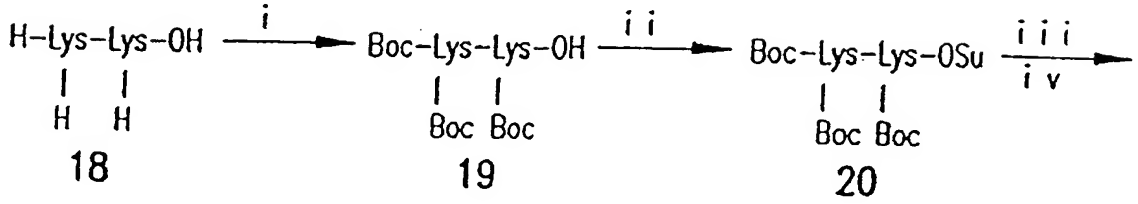
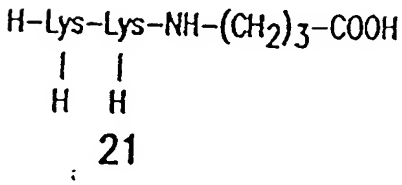


FIG. 4

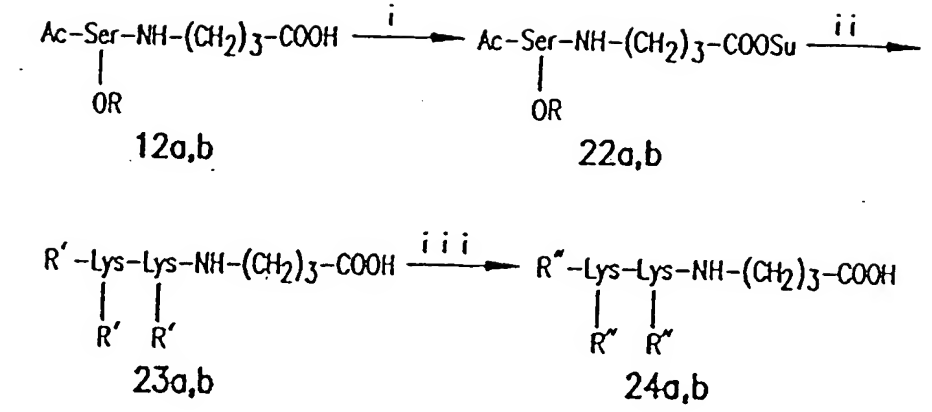
PREPARATION OF CORE STRUCTURE





Reagents: i) Boc_2O, Et_3N, MeOH; i i) NHS, EDC, CH_2Cl_2;
i i i) $H_2N-(CH_2)_3-COOH$, Et_3N, DMF; iv) HCOOH.

FIG. 5A



Reagents: i) NHS, EDC, DMF; i i) 21, Et_3N, DMF–H_2O;
i i i) 10% 1N NaOH in MeOH, 5 min.

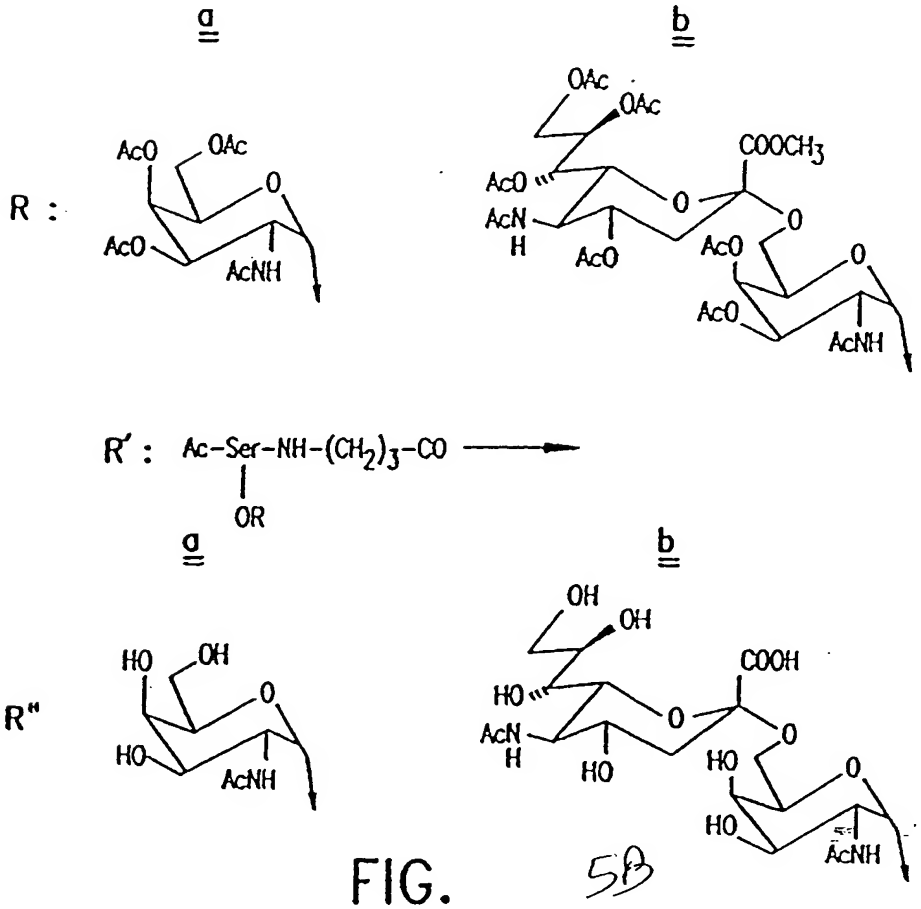
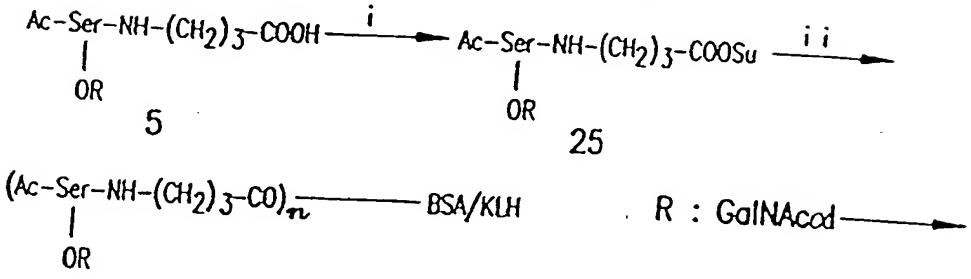


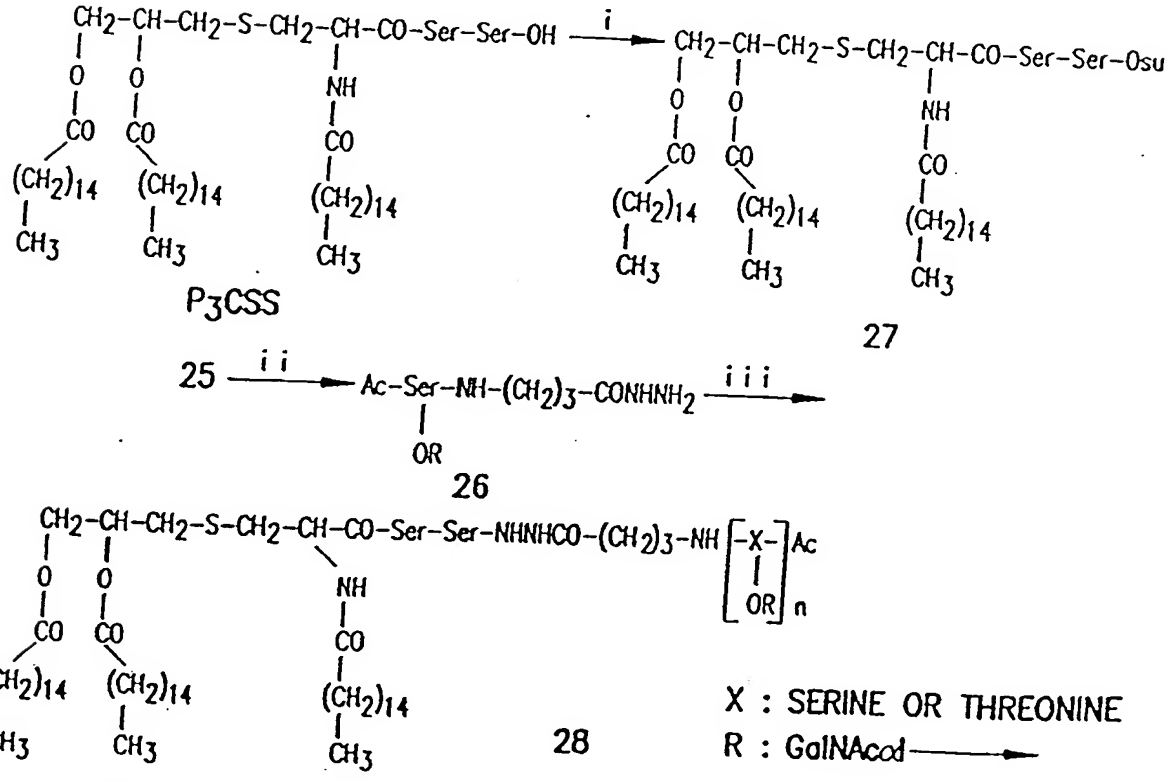
FIG. 5B

CONJUGATION WITH CARRIER PROTEINS



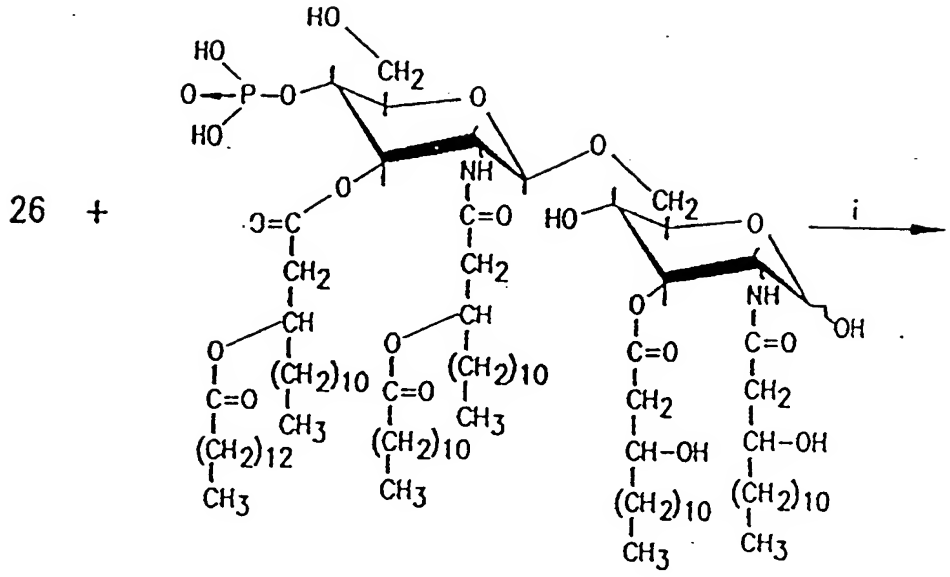
Reagents: i) NHS, EDC, DMF; ii) BSA/KLH, $NaHCO_3$, DMF-H_2O.

CONJUGATION WITH NON-MACROMOLECULES

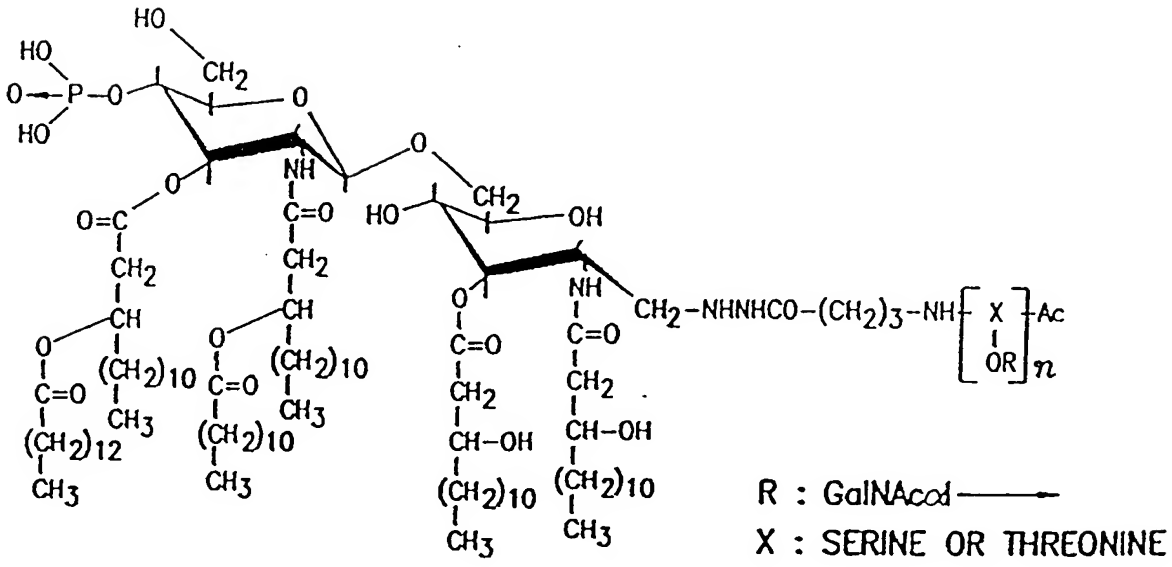


Reagents: i) NHS, EDC, CH_2Cl_2; ii) NH_2NH_2, aq MeOH; iii) DMF-H_2O.

FIG. 6A



MPL



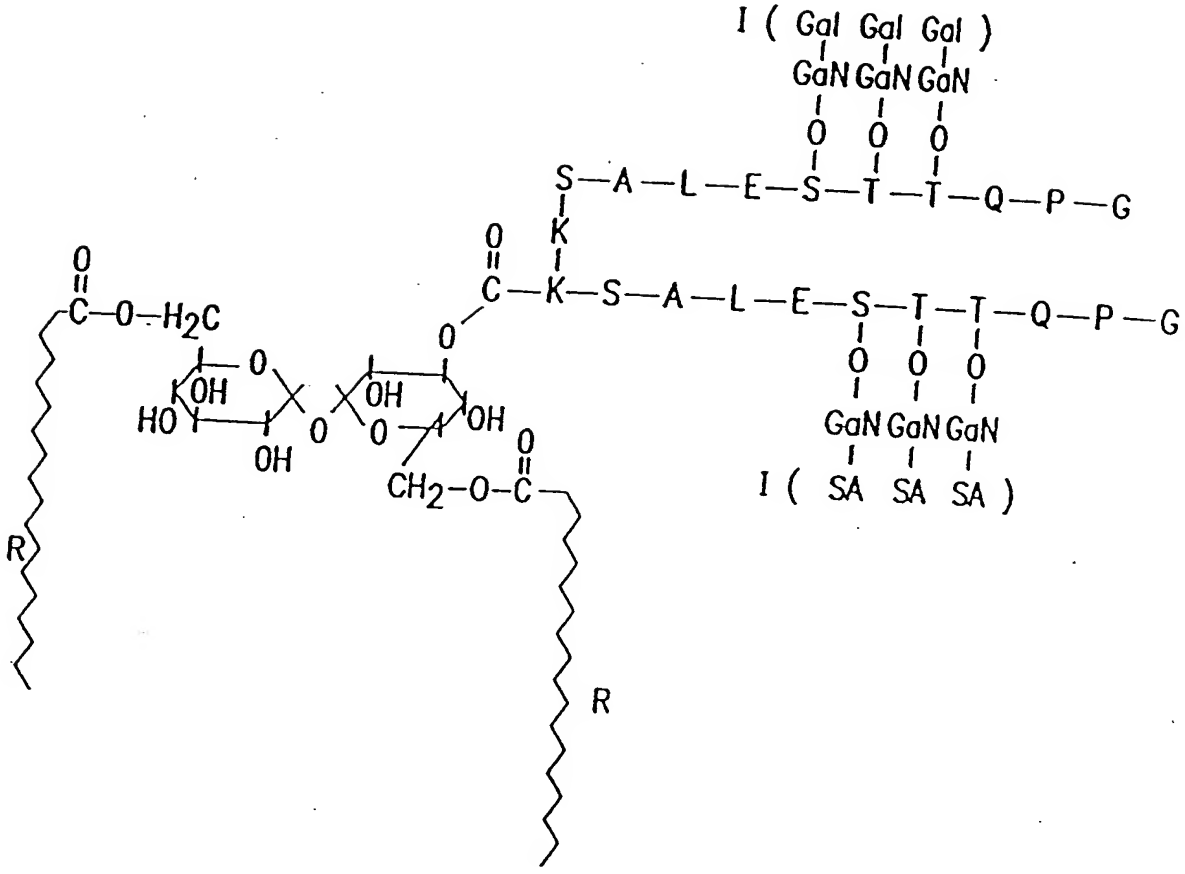
R : GalNAcα1 ——→

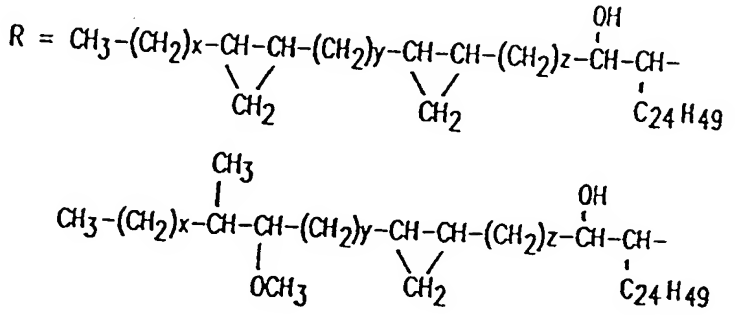
X : SERINE OR THREONINE

29

Reagents: i) $NaCNBH_3$, $NaHCO_3$, H_2O.

FIG. 6B





In general, x,y,z are odd, even and odd number; e.g. 17,14,17

FIG. 6A

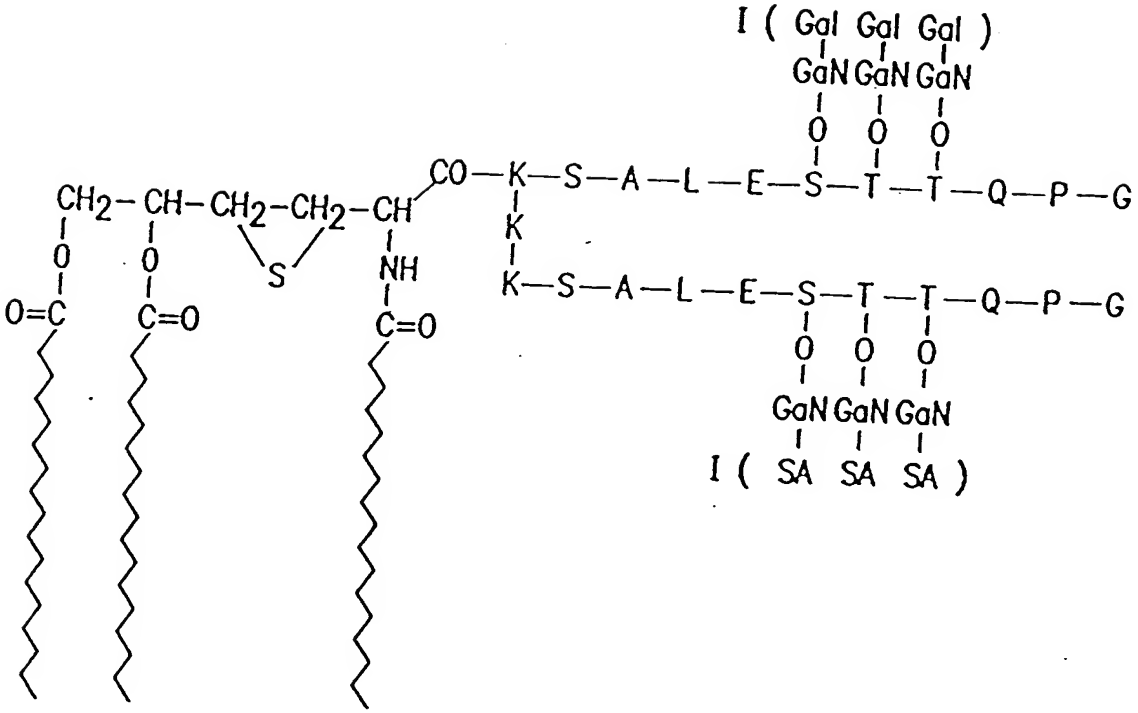
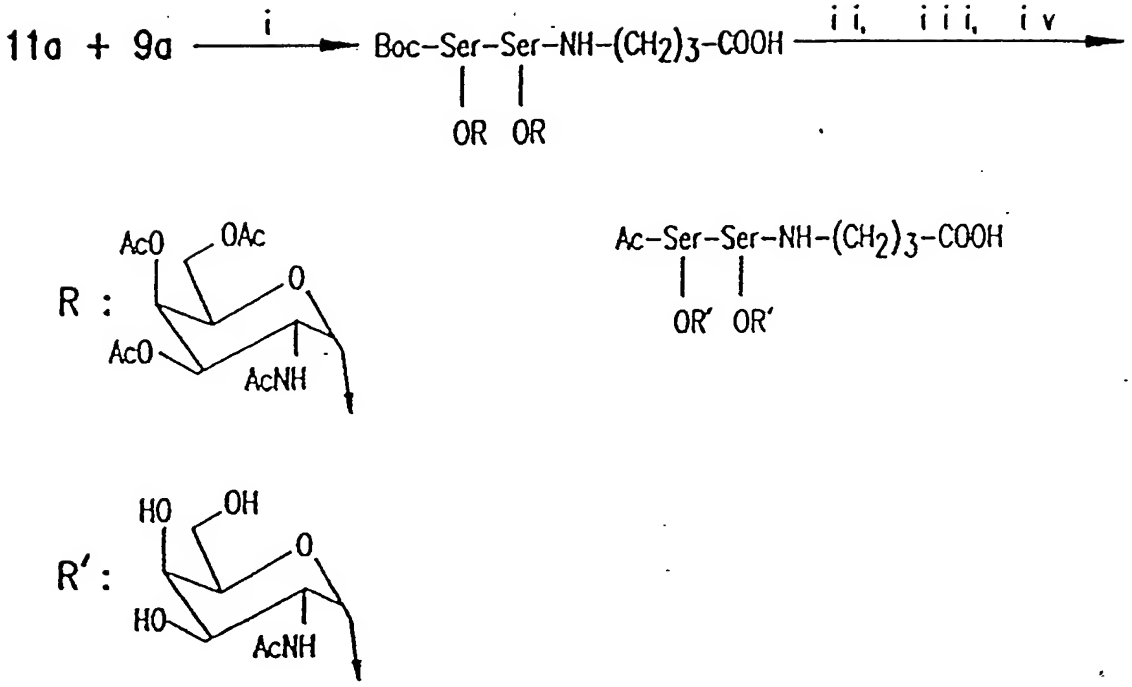

I (Gal Gal Gal)
GaN GaN GaN
O O O
CO—K—S—A—L—E—S—T—T—Q—P—G
K
K—S—A—L—E—S—T—T—Q—P—G
O O O
GaN GaN GaN
I (SA SA SA)
CH2—CH—CH2—CH2—CH
O O
O=C C=O
S
NH
C=O

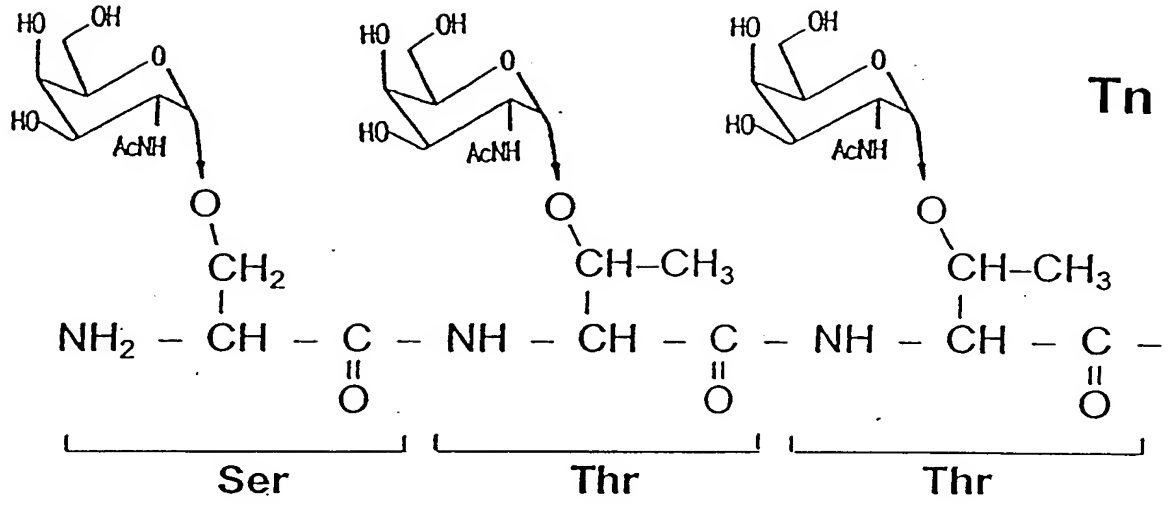
FIG. 7B



Reagents: i) Et_3N, DMF; ii) HCOOH; iii) Ac_2O, MeOH; iv) 10% 1N NaOH–MeOH, 5 min.

FIG. 8

Fig.9A



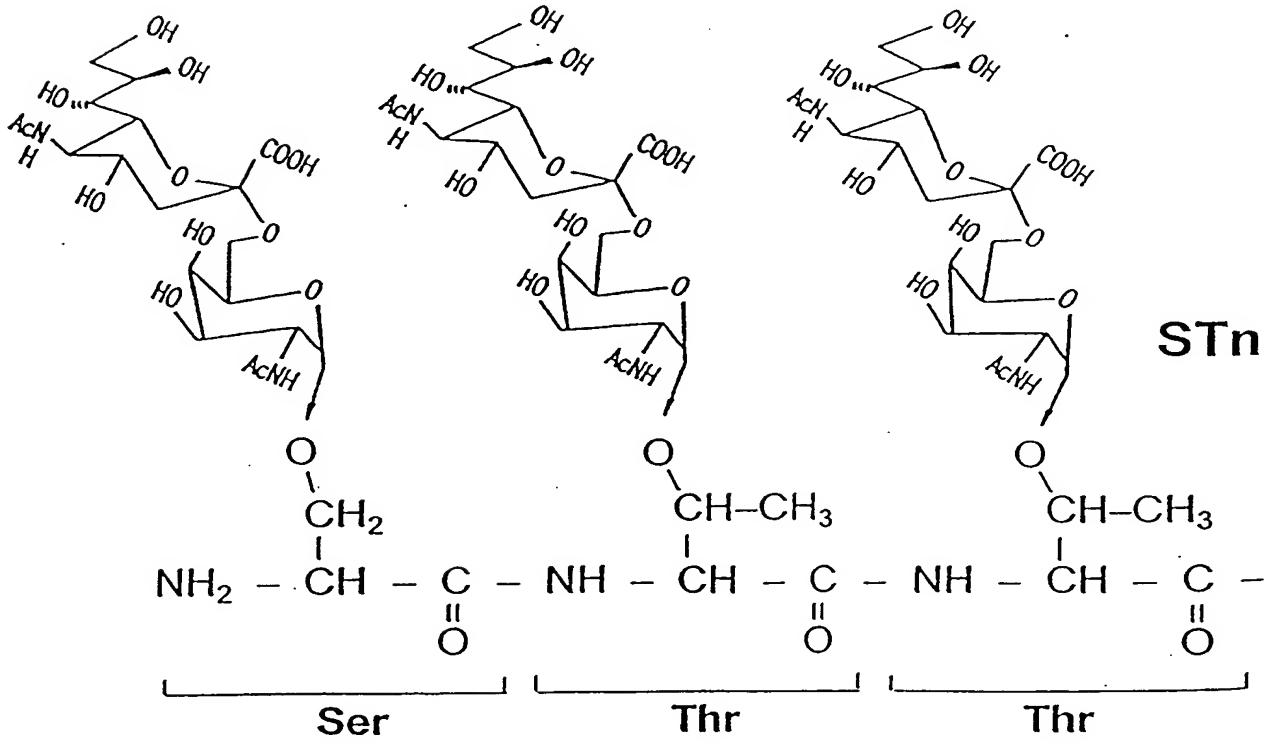
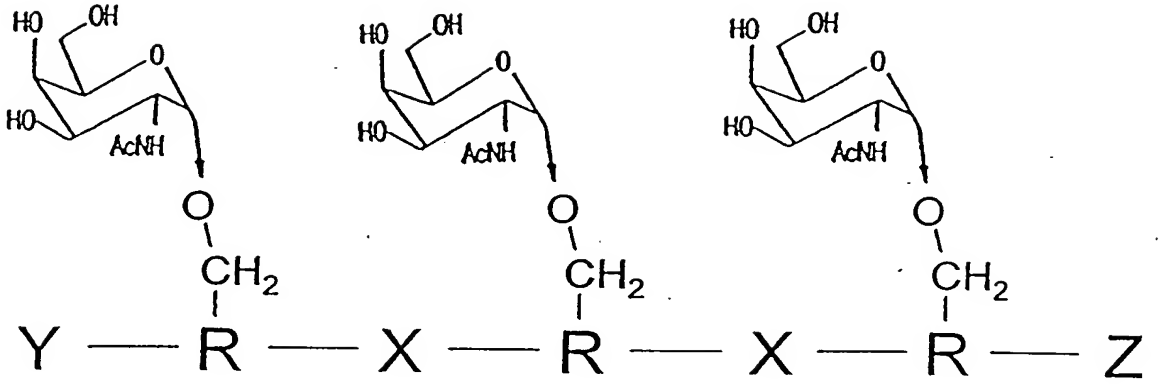


Fig.9B



Y = terminal protected residue. X = spacer.
Z = active functional group ready to link to core or carrier molecule (*e.g.* activated carboxyl)

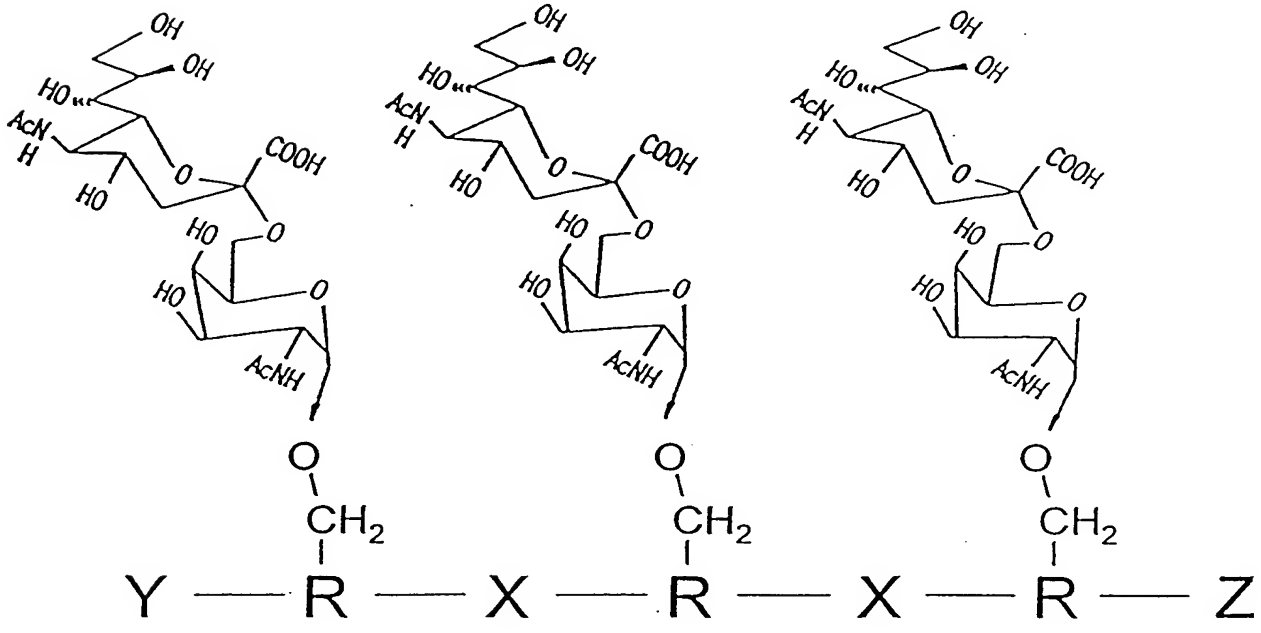
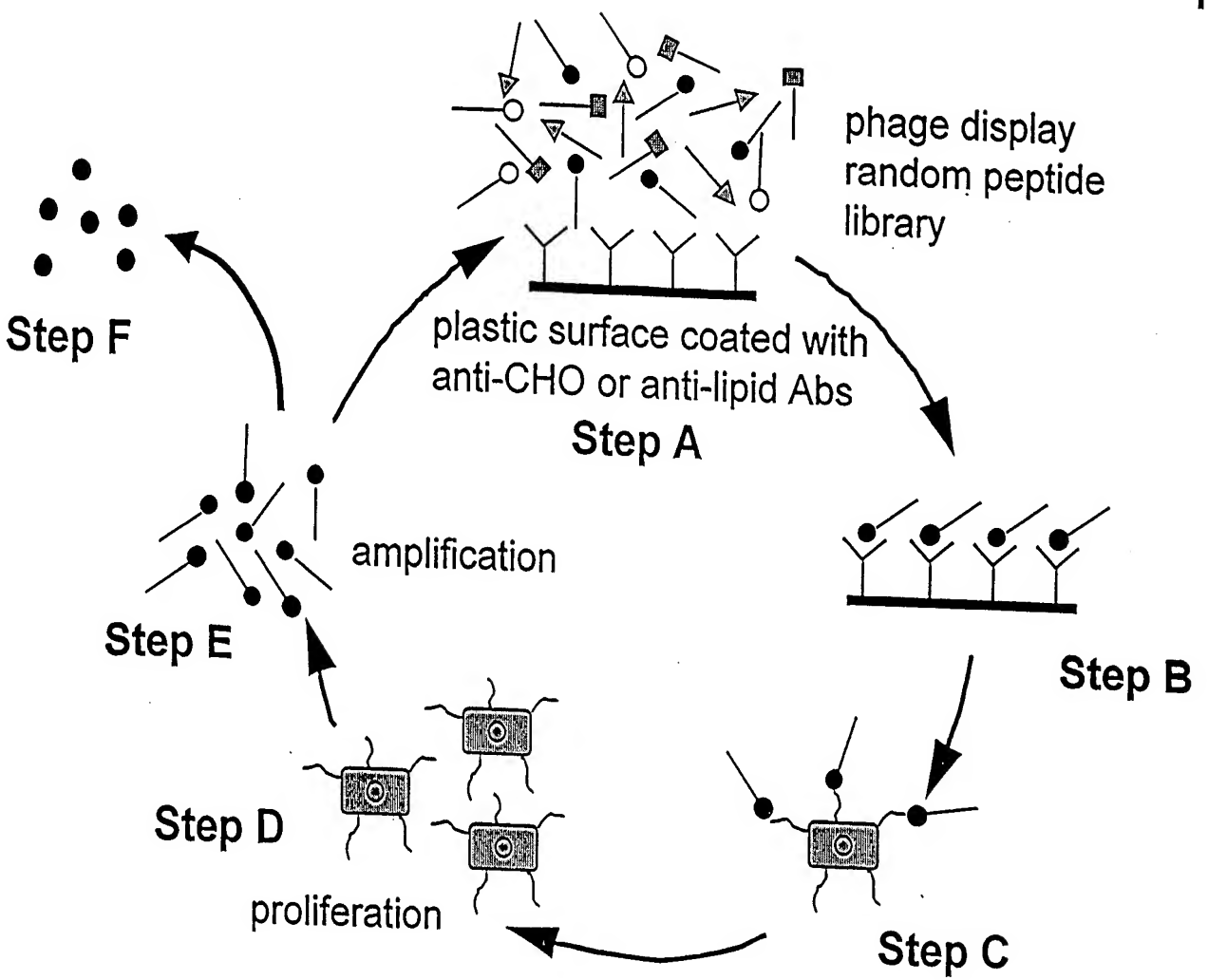


Figure 10



Cycle is repeated 4-5 times

Figure 11A. Class II MHC restricted presentation of extracellular antigen to CD4+ T helper cells.

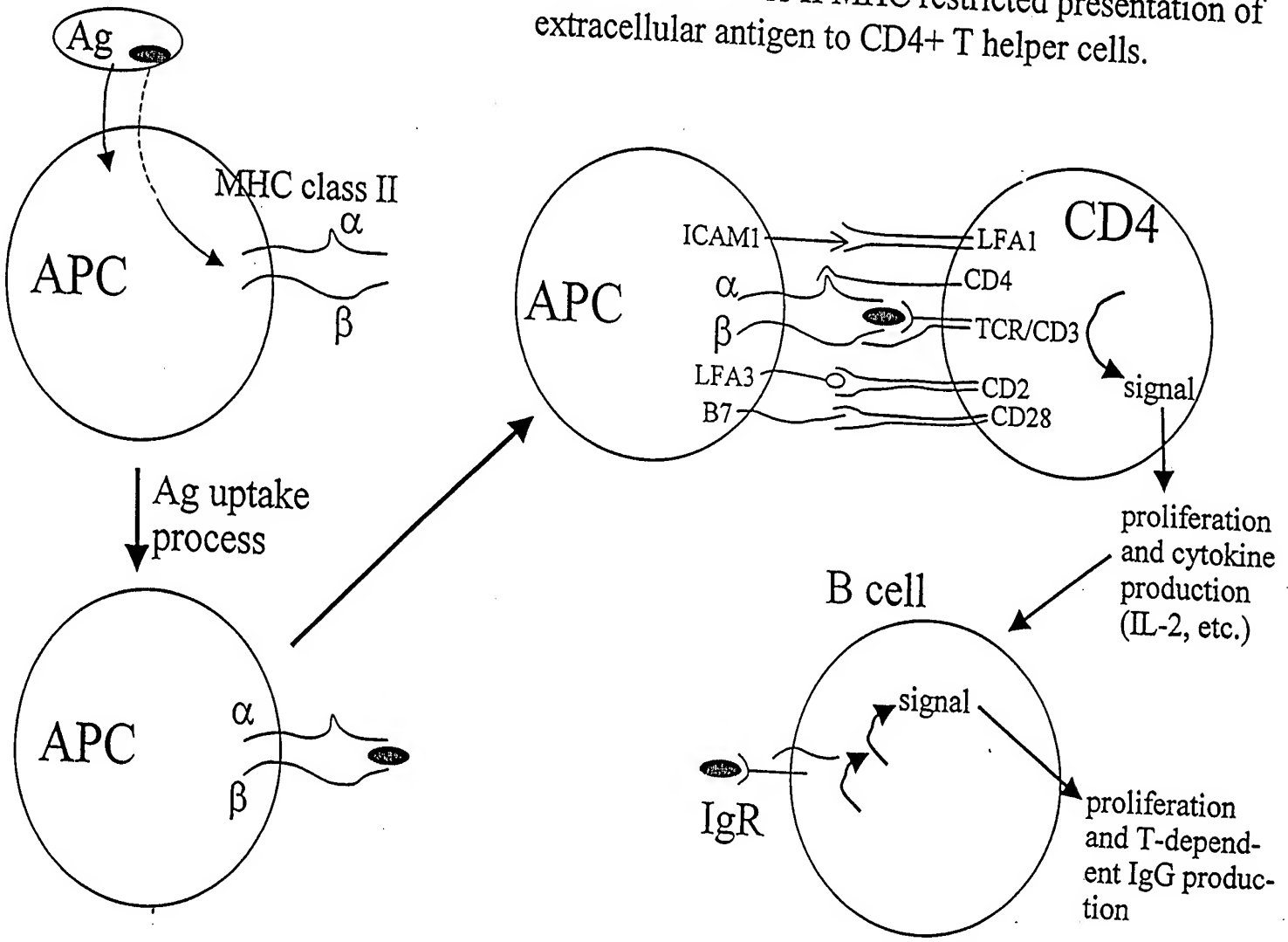


Fig. 12

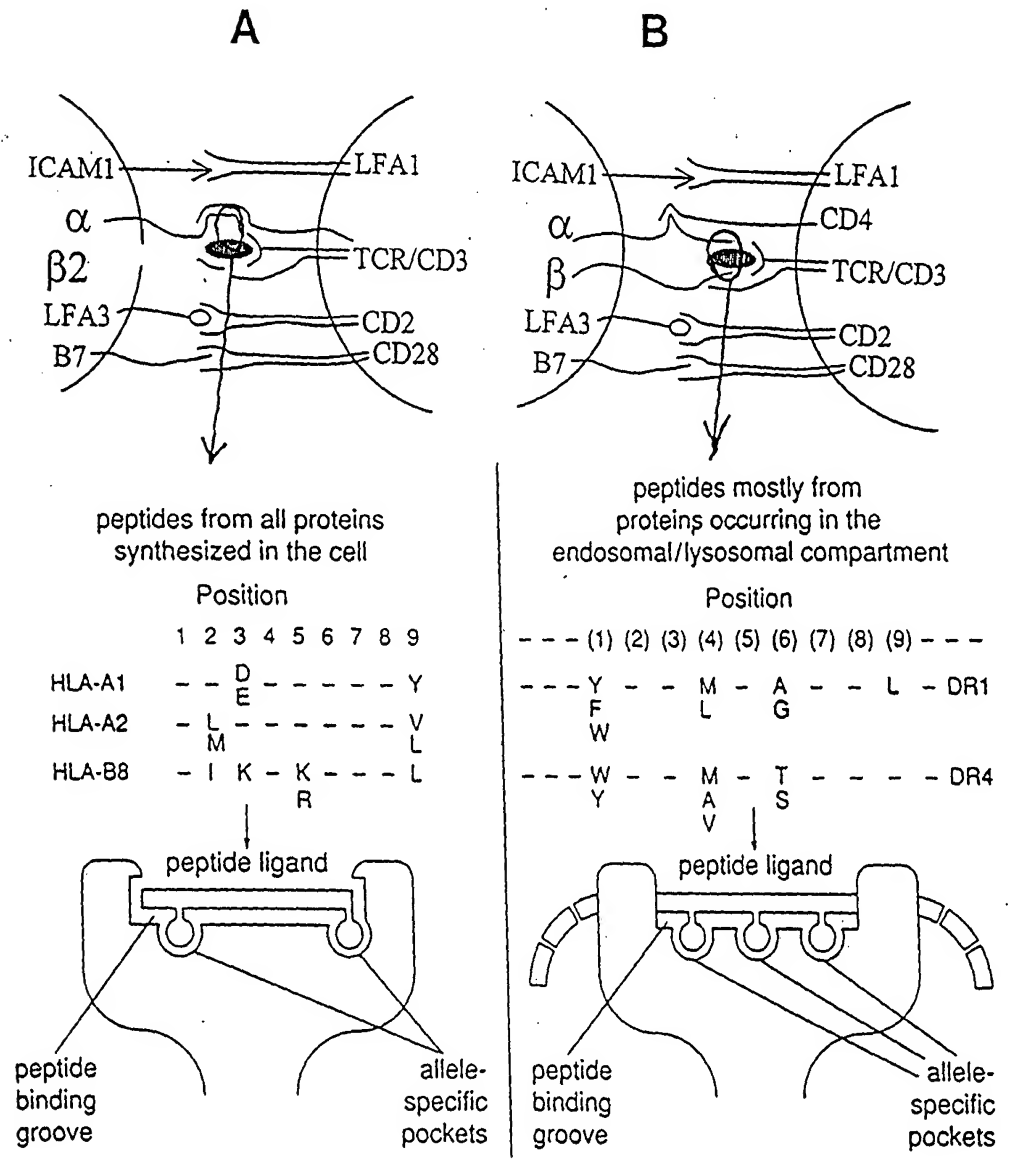
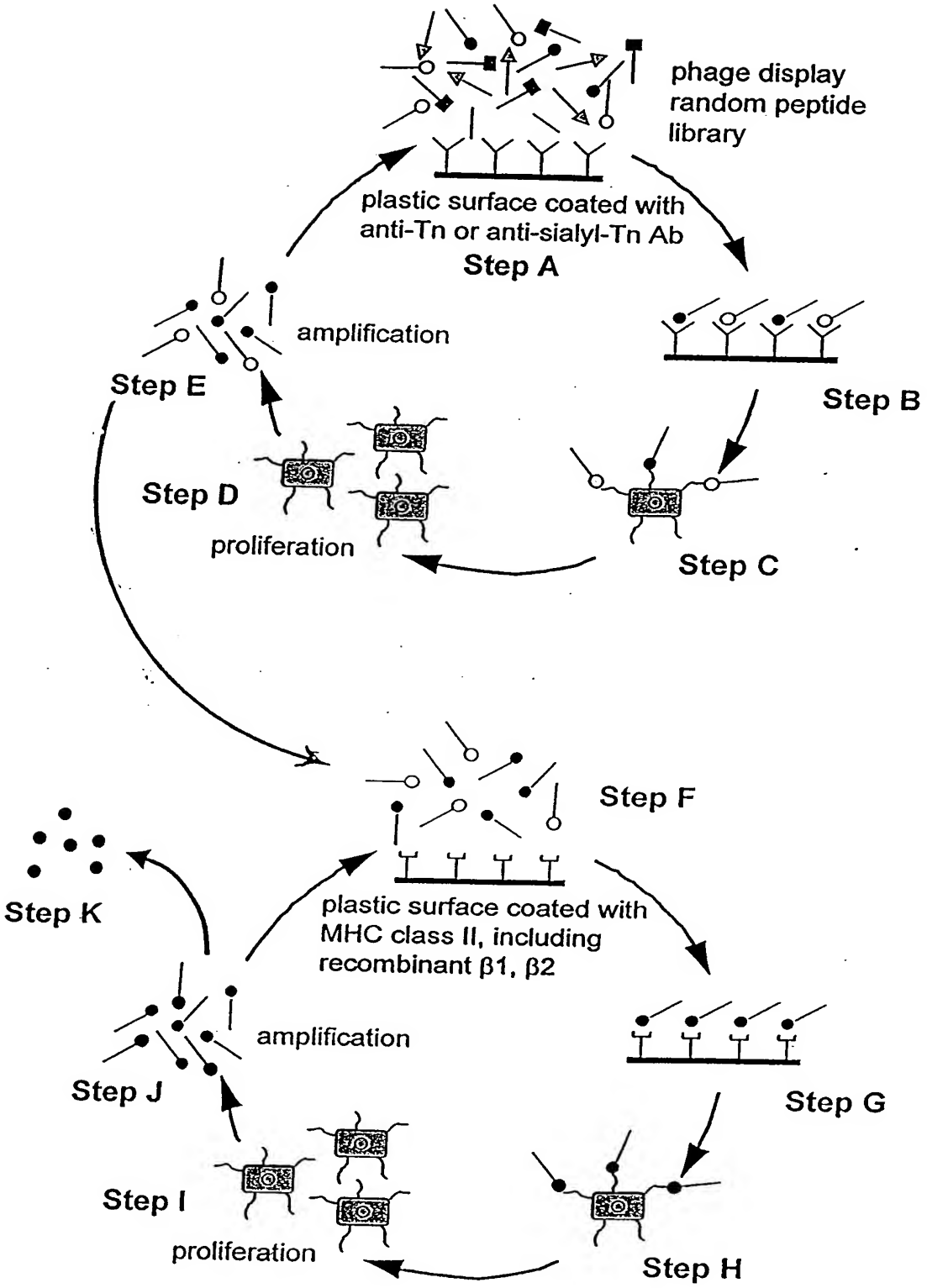

A
B
ICAM1
LFA1
α
β2
TCR/CD3
LFA3
CD2
B7
CD28
ICAM1
LFA1
α
CD4
β
TCR/CD3
LFA3
CD2
B7
CD28
peptides from all proteins synthesized in the cell
Position
1 2 3 4 5 6 7 8 9
HLA-A1 – – D/E – – – – – Y
HLA-A2 – L/M – – – – – – V/L
HLA-B8 – I K – K/R – – – L
peptide ligand
peptide binding groove
allele-specific pockets
peptides mostly from proteins occurring in the endosomal/lysosomal compartment
Position
– – – (1) (2) (3) (4) (5) (6) (7) (8) (9) – – –
– – – Y/F/W – – M/L – A/G – – L – DR1
– – – W/Y – – M/A/V – T/S – – – – DR4
peptide ligand
peptide binding groove
allele-specific pockets

Figure 13



for CIP Feb 99, Fig 13